EVALUATION OF THE RIVAROXABAN-INFLUENCED EFFECT OF *ABCB1* AND *CYP3A5* GENE POLYMORPHISMS ON PROTHROMBIN TIME IN PATIENTS AFTER TOTAL HIP OR KNEE REPLACEMENT SURGERY

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Rivaroxaban is a safer and more effective alternative to warfarin. However, there are reports of some cases of major hemorrhagic complications associated with rivaroxaban that significantly impair the patients' quality of life and can lead to a fatality. Personalized therapy, including pharmacogenetic testing, may help prevent such adverse events. This study aimed to investigate how *ABCB1* 3435C>T (rs1045642) and *CYP3A5* 6986A>G (rs776746) gene polymorphisms, when carried by a patient taking rivaroxaban to prevent thrombosis after total hip or knee replacement surgery, affect prothrombin time (PT). Sixty-five patients participated in the study. Their genotypes were identified by PCR in real time. To learn PT peculiar to each patient, we collected venous blood on the 5th day of their anticoagulation therapy, 1 hour before they took rivaroxaban and 3 hours after. Having calculated %ΔPT, we divided the patients into 2 groups: 1) %ΔPT ≤ 0 (n = 7; 10.8%); 2) %ΔPT > 0 (n = 58; 89.2%). Regarding the distribution of rs1045642 polymorphism, we determined the difference between the groups to be statistically significant (χ^2 = 6.64; p = 0.027). As for rs776746 polymorphism, the difference was insignificant (χ^2 = 0.101; p = 1.0). We discovered that rs1045642 polymorphism has a significant effect on PT variance in patients taking rivaroxaban to prevent thrombosis after total hip or knee replacement surgery.

Keywords: rivaroxaban, pharmacogenetics, prothrombin time, hip replacement surgery, knee replacement surgery, thromboprophylaxis

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ОЦЕНКА ВЛИЯНИЯ ПОЛИМОРФИЗМОВ ГЕНОВ *ABCB1* И *CYP3A5* НА СТЕПЕНЬ ИЗМЕНЕНИЯ ПРОТРОМБИНОВОГО ВРЕМЕНИ ПОД ВЛИЯНИЕМ РИВАРОКСАБАНА У ПАЦИЕНТОВ ПОСЛЕ ЭНДОПРОТЕЗИРОВАНИЯ КРУПНЫХ СУСТАВОВ НИЖНИХ КОНЕЧНОСТЕЙ

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Несмотря на высокую эффективность и безопасность применения ривароксабана по сравнению с варфарином, в клинической практике наблюдаются редкие случаи крупных геморрагических осложнений, которые могут значительно ухудшать качество жизни пациентов или быть летальными. Остается открытым вопрос, насколько фармакогенетические тесты позволят профилактировать развитие таких неблагоприятных событий. Целью работы было оценить влияние носительства полиморфизмов *ABCB1* 3435C>T (rs1045642) и *CYP3A5* 6986A>G (rs776746) на изменение протромбинового времени (ПВ) у пациентов, принимающих для тромбопрофилактики ривароксабан после эндопротезирования крупных суставов нижних конечностей. В исследование были включены 65 пациентов. Генотипирование проводили с помощью ПЦР в реальном времени. Для определения ПВ венозную кровь отбирали на 5 сутки приема антикоагулянта 2 раза: за 1 ч до приема ривароксабана и через 3 ч после приема. Вычислив %ΔПВ, пациентов делили на 2 группы: 1) %ΔПВ ≤ 0 (n = 7; 10,8%); 2) %ΔПВ > 0 (n = 58; 89,2%). Между группами %ΔПВ относительно распределения генотипов полиморфизма rs1045642 была определена статистически достоверная разница (χ^2 = 6,64; p = 0,027). Относительно распределения генотипов полиморфизма rs776746 статистически значимой разницы между группами %ΔПВ обнаружено не было (χ^2 = 0,101; p = 1,0). Выявлено статистически значимое влияние полиморфизма rs1045642 на характер изменения ПВ у пациентов, принимающих с целью тромбопрофилактики ривароксабан после эндопротезирования крупных суставов нижних конечностей.

Ключевые слова: ривароксабан, фармакогенетика, протромбиновое время, эндопротезирование тазобедренного сустава, эндопротезирование коленного сустава, тромбопрофилактика

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Deep vein thrombosis (DVT) and pulmonary embolism (PE) are some of the most important problems encountered by practitioners. PE risk group includes patients after hip or knee replacement surgery. About 50–60% of THR (total hip replacement surgery) and TKR (total knee replacement surgery) patients that receive no thrombosis prevention therapy have DVT after surgery [1]. Approximately 1 in every 500 THR patients can have a fatal PE [2]. The number of THRs in Russia is increasing every year; currently, about 25 persons in each 100,000 have THRs [3].

Direct oral anticoagulants (DOACs) have recently been approved for the prevention of venous thromboembolism (VTE) in patients after elective hip or knee arthroplasty. DOACs have demonstrated acceptable efficacy and safety profiles. These drugs require no laboratory control. This article focuses on rivaroxaban, which is a direct factor Xa inhibitor. The anticoagulant got the FDA approval in 2011 as a medication to prevent thrombosis in patients after elective hip or knee arthroplasty [4].

About 18% of the rivaroxaban dose is metabolized by CYP3A4/5, 14% — by CYP2J2.

Approximately 36% of the dose is excreted via kidney in form of the unchanged drug, involving the active transporter-mediated secretion by P-glycoprotein (P-gp) and BCRP (Breast Cancer Resistance Protein) [5].

P-gp is a large membrane protein that transports drugs from inside the cell. It is found on the surface of epithelial cells lining small and large intestines, pancreatic duct, in the liver's bile vessels membrane, proximal kidney tubules and adrenal glands, as well as in endothelial cells of blood-tissue interfaces (brain-blood, blood-follicle, blood-testis, and blood-placental barriers) [6]. P-gp is encoded by the *ABCB1* gene located on chromosome 7 (7q21.12) [7]. The most common single nucleotide polymorphisms (SNPs) of the *ABCB1* gene are 1236T> C (rs1128503), 2677T> G / A (rs2032582) and 3435T> C (rs1045642) [8]. In this study, we focused on the impact of the *ABCB1* 3435C>T polymorphism (rs1045642).

Jointly, CYP3A4 and CYP3A5 proteins account for about 30% of hepatic cytochrome P450; about half of the drugs metabolized by cytochrome P450 are CYP3A substrates. *CYP3A4* and *CYP3A5* are expressed in liver and intestines, with *CYP3A5* expression seen mostly in extrahepatic tissues. The *CYP3A5* gene is located on chromosome 7 (7q22.1); it encodes the protein of 502 amino acids. The most common SNP of the *CYP3A5* gene is 6986A>G (rs776746). It should be noted here that *CYP3A5* 6986GG genotype carriers do not fully express the *CYP3A5* isoenzyme [9].

According to the RECORD 1-4 research program [10–13], despite the good efficacy and safety profiles of rivaroxaban when prescribed to prevent thrombosis after hip or knee replacement surgery, 2.87% of patients exhibited nonmajor clinically relevant bleeding, including hematomas in the area of surgery that may be infected. Such complications require removal of the endoprosthesis, which worsens the patient's quality of life and translates into an additional financial burden for the health care system. Currently, practitioners resort to the personalized therapy, including pharmacogenetic testing, to prevent such adverse events.

This study aimed to investigate how the *ABCB1* 3435C>T (rs1045642) and *CYP3A5* 6986A>G (rs776746) gene polymorphisms, when carried by a patient taking rivaroxaban to prevent thrombosis after total hip or knee replacement surgery, the affect prothrombin time (PT).

METHODS

The study protocol was reviewed and approved by the local ethics committee of I. M. Sechenov First Moscow State Medical University (Sechenov University) (meeting minutes #03-17 of 2017.04.19). The inclusion criteria were: any gender; age ≥18 years; primary TKR or THR performed; thrombosis prevention therapy — 10 mg rivaroxaban OD; informed voluntary consent. The exclusion criteria were: atrial fibrillation with anticoagulant therapy; hemorrhagic diathesis; acute intracranial disease or hemorrhagic stroke recorded in the past three months; gastrointestinal bleeding, hematuria, peptic ulcer or duodenal ulcer recorded in the last 6 months; severe liver disease; liver transaminases (GPT and GOT) ≥2 upper limits of the norm in the last month; severe renal impairment (CK <30 ml/min); advanced stage of cancer; pregnancy, lactation; age <18 years.

Sixty-five persons participated in the study, 19 THR patients (29.2%) and 46 TKR patients (70.8%). They were 48 (73.8%) women and 17 (26.2%) men aged 24 to 83 years (mean age — 59 ± 12 years). Following the instructions detailing the use of the medicine for the purposes of post-surgery thrombosis prevention, the patients took 10 mg rivaroxaban once a day. THR patietns received the medicine for 35 days, TKR patients — for 14 days [14].

We purified DNA from the patients' venous blood. For the purposes of genotyping, the blood was collected into 4 ml Vacuette® vacuum tubes with EDTA-K3 anticoagulant. Real-time polymerase chain reaction (PCR) allowed genotyping *ABCB1* 3435C>T (rs1045642) and *CYP3A5* 6986A>G (rs776746) polymorphisms; we used the CFX96 Touch™ Real-Time PCR Detection System DNA amplifier (Bio-Rad Laboratories, Inc.; USA) at Research and Development center of the Russian Medical Academy of Continuous Professional Education of the Ministry of Health of Russia.

PT was the indicator reflecting the rivaroxaban's pharmacodynamic properties; to learn it, we collected venous blood of the patients on the 5th day of their anticoagulation therapy, 1 hour before they took the medicine (PT_1) and 3 hours after (PT_2), into 2.7 ml BD Vacutainer® vacuum tubes with 3.2% sodium citrate. PT was determined manually, using Tekhplastin-test (Tekhnologiya-Standard; Russia) in accordance with the manufacturer's instructions.

The formula $\%\Delta PT = (PT_2 - PT_1) / PT_1 \times 100\%$ allowed finding the differences between PT values through calculating %ΔPT, which governed the division of patients into two %ΔPT groups: 1) patients with $\%\Delta PT \leq 0$; 2) patients with $\%\Delta PT > 0$.

The studied polymorphism genotypes frequency distribution was tested for compliance with the Hardy–Weinberg equilibrium using an online calculator [15]. To determine the difference between the groups as conditioned by the impact of *ABCB1* 3435C>T (rs1045642) and *CYP3A5* 6986A>G (rs776746) polymorphisms, we ran the chi-square test for independence. PASW Statistics 18 (2009) software was used to process the results.

RESULTS

Based on the *ABCB1* 3435C>T (rs1045642) polymorphism genotype, the patients were divided into 3 groups: 1) 3435CC genotype, $n = 17$ (26.2%); 2) 3435CT genotype, $n = 27$ (41.5%); 3) 3435TT genotype, $n = 21$ (32.3%). As for the *CYP3A5* 6986A>G (rs776746) polymorphism genotypes, we found 7 patients (10.8%) with 6986AG genotype (10.8%) and 58 patients (89.2%) with 6986GG genotype (Table 1).

The *ABCB1* 3435C>T (rs1045642) and *CYP3A5* 6986A>G polymorphism genotypes distributions were within the Hardy–Weinberg equilibrium, ($\chi^2 = 1.79$; $p = 0.409$ and $\chi^2 = 0.21$; $p = 0.9$, respectively).

Among the patients participating in the study, the mean PT_1 value (measured 1 hour before administration of rivaroxaban) was 15.5 ± 4.1 seconds, and the mean PT_2 value (measured 3 hours after administration of rivaroxaban) was 19.1 ± 3.2 seconds. Table 2 shows other mean PT values through the lens of their dependence on the *ABCB1* 3435C>T (rs1045642) and *CYP3A5* 6986A>G (rs776746) polymorphism genotypes.

Case-wise analysis of the PT variability revealed 7 patients (10.8%) that had a paradoxical reaction, i.e. after administration of rivaroxaban the PT in them either grew smaller or did not change (%ΔPT ≤ 0). In the remaining 58 patients (89.2%) rivaroxaban made the PT greater, as expected (%ΔPT > 0). 6 patients (85.7%) were carrying the *ABCB1* 3435CT genotype and none — the *ABCB1* 3435TT genotype in the group with %ΔPT ≤ 0. The chi-square test for independence revealed a statistically significant difference between %ΔPT groups as conditioned by the distribution of the *ABCB1* 3435C>T (rs1045642) polymorphism genotypes ($\chi^2 = 6.64$; $p = 0.027$) (Table 3).

Patients with the *ABCB1* 3435CT genotype contributed the most to the difference between %ΔPT groups. Table 4 presents "manual" determination of reliability of differences in the set of frequencies, which allows seeing the reasons behind the main difference.

As for the *CYP3A5* 6986A>G (rs776746) polymorphism genotypes, there were no significant differences in their distribution among %ΔPT groups ($\chi^2 = 0.101$; $p = 1.0$) (Table 5).

DISCUSSION

Drugs as P-gp substrates are widely used in the routine clinical practice, which is why studying the effect *ABCB1* gene polymorphisms have on pharmacodynamic and pharmacokinetic qualities of medications is a matter of great interest.

Today, many researchers investigate the impact of *ABCB1* gene polymorphisms on the pharmacodynamic properties of various medicines. One of the efforts was aimed at studying the relationship between *ABCB1* 3435C>T polymorphism and response to antiretroviral therapy in HIV-1 patients (n = 123) that received efavirenz or nelfinavir [16]. The authors of that research found that patients with the 3435T allele respond to antiretroviral therapy better. Another work revealed no link between the *ABCB1* 3435C>T (rs1045642) polymorphism and virological, immunological responses to antiretroviral therapy [17].

P-gp also transports antiepileptic drugs [18]. Genotyping epilepsy patients (n = 315) by the *ABCB1* 3435C>T (rs1045642) polymorphism, the researchers discovered that those resistant to antiepileptic pharmacotherapy are more likely to carry the *ABCB1* 3435CC genotype as opposed to the patients whose response to such therapy was positive [19].

CYP3A5 gene polymorphism can contribute to the variability of *CYP3A5* substrates clearance. Studying the effect *CYP3A5* expression has on the pharmacological response of statins, the researchers have shown that lovastatin, simvastatin and atorvastatin are significantly less effective in *CYP3A5* expressors than in non-expressors [20].

In the context of our work, which also addressed the impact of *ABCB1* and *CYP3A5* genes polymorphisms on the pharmacodynamic properties of a drug — rivaroxaban, in our case, — we have revealed a statistically significant difference in distribution of *ABCB1* 3435C> T (rs1045642) polymorphism genotypes between %ΔPT groups, one with %ΔPT ≤ 0 and another with %ΔPT > 0. The difference mainly originates with

Table 1. Distribution of *ABCB1* 3435C>T (rs1045642) and *CYP3A5* 6986A>G (rs776746) polymorphisms genotypes in THR and TKR patients receiving rivaroxaban

Polymorphisms	Genotype	Number of patients	
		absolute	relative, %
ABCB1 3435C>T (rs1045642)	*ABCB1* 3435CC	17	26.2
	ABCB1 3435CT	27	41.5
	ABCB1 3435TT	21	32.3
CYP3A5 6986A>G (rs776746)	*CYP3A5* 6986AG	7	10.8
	CYP3A5 6986GG	58	89.2

Table 2. Mean PT values by group and as conditioned by the *ABCB1* 3435C>T (rs1045642) and *CYP3A5* 6986A>G (rs776746) polymorphism genotypes in THR and TKR patients receiving rivaroxaban

	Mean PT_1, s	Mean PT_2, s	p	Mean ΔPT, s	Mean %ΔPT, %
Participating patients (n = 65)	15.5 ± 4.1	19.1 ± 3.2	$t = 9.185$ $p = 2.7 \times 10^{-13}$	3.6 ± 4.9	27.4 ± 26.3
ABCB1 3435CC	14.8 ± 2.1	19.8 ± 3.7	$t = 5.48$ $p = 5.03 \times 10^{-5}$	4.95 ± 3.3	34.7 ± 24.5
ABCB1 3435CT	16.0 ± 5.7	18.4 ± 3.0	$t = 4.074$ $p = 3.85 \times 10^{-4}$	2.4 ± 6.8	22.8 ± 32.9
ABCB1 3435TT	15.5 ± 2.8	19.5 ± 2.7	$t = 6.652$ $p = 1.77 \times 10^{-6}$	4.02 ± 2.2	27.3 ± 15.8
CYP3A5 6986AG	14.3 ± 1.9	20.6 ± 3.1	$t = 5.358$ $p = 0.002$	6.3 ± 4.2	47.3 ± 34.8
CYP3A5 6986GG	15.7 ± 4.3	18.9 ± 3.1	$t = 7.798$ $p = 1.49 \times 10^{-10}$	3.2 ± 4.95	25.0 ± 24.3

Table 3. Distribution of *ABCB1* 3435C>T (rs1045642) polymorphism genotypes, %ΔPT groups, THR and TKR patients receiving rivaroxaban (n = 65)*

	%ΔPT ≤ 0	%ΔPT > 0
ABCB1 3435CC	1 (14.3%)	16 (27.6%)
ABCB1 3435CT	6 (85.7%)	21 (36.2%)
ABCB1 3435TT	0 (0%)	21 (36.2%)

Note: * $\chi^2 = 6.64$; $p = 0.027$.

Table 4. Determination of significance of differences between observed and expected distribution of *ABCB1* 3435C>T (rs1045642) polymorphism genotypes, %ΔPT groups

Observed genotypes distribution, %ΔPT groups			
	%ΔPT ≤ 0	%ΔPT > 0	Total
ABCB1 3435CC	1	16	17
ABCB1 3435CT	6	21	27
ABCB1 3435TT	0	21	21
Total	7	58	65
Expected genotypes distribution, %ΔPT groups			
	%ΔPT ≤ 0	%ΔPT > 0	Total
ABCB1 3435CC	2	15	17
ABCB1 3435CT	3	24	27
ABCB1 3435TT	2	19	21
Total	7	58	65
Significant difference between observed and expected genotypes distribution			
	%ΔPT ≤ 0	%ΔPT > 0	Total
ABCB1 3435CC	0.50	0.07	0.57
ABCB1 3435CT	3.00	0.38	3.38
ABCB1 3435TT	2.00	0.21	2.21
Total	5.50	0.66	6.16

Table 5. Distribution of *CYP3A5* 6986A>G (rs776746) polymorphism genotypes, %ΔPT, THR and TKR patients receiving rivaroxaban (n = 65)*

	%ΔPT ≤ 0	%ΔPT > 0
CYP3A5 6986AG	1 (14.3%)	6 (10.3%)
CYP3A5 6986GG	6 (85.7%)	52 (89.7%)

Note: * χ^2 = 0.101; p = 1.0

the patients carrying the *ABCB1* 3435CT genotype (85.7%) that belong to the %ΔPT ≤ 0 group; this may point to the necessity to adjust the dose for such people, since the standard dose of rivaroxaban may have no clinical effect in them.

The majority (89.2%) of patients participating in our study had the *CYP3A5* 6986GG genotype; the CYP3A5 isoenzyme was not fully expressed in their bodies. As for the distribution of *CYP3A5* 6986A>G (rs776746) polymorphism genotypes in the %ΔPT groups, the difference between them was insignificant, which presumably signals of the role of *CYP3A5* isoenzyme in rivaroxaban pharmacokinetics being inferior to that of the P-gp membrane transporter.

Considering the discovered effect *ABCB1* 3435C>T (rs1045642) polymorphism has on %ΔPT under the influence of rivaroxaban, we believe it is important to research not only pharmacodynamics, but also pharmacokinetics of rivaroxaban in patients with different genotypes.

CONCLUSIONS

We discovered that *ABCB1* 3435C>T (rs1045642) polymorphism has a statistically significant effect on PT variance in THR and TKR patients taking rivaroxaban to prevent thrombosis. There was found no statistically significant dependence of %ΔPT on *CYP3A5* 6986A>G (rs776746) polymorphism. We believe it is necessary to study both pharmacodynamics and pharmacokinetics of rivaroxaban in patients with different genotypes.

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